Reversing Blindness with New FDA Approved Retinal Gene Therapy

In December 2017, the FDA approved a DNA altering medication that can reverse an inherited form of progressive blindness. Luxturna is a gene therapy which can treat a condition called Leber's Congenital Amaurosis (LCA) wherein people have inherited two faulty copies of the RPE65 gene. The therapy replaces those faulty genes with normal versions, thus erasing the mutations' harmful effects. A single injection in each eye has shown to be enough to improve lost vision. We are talking to the doctor couple, Dr. Jean Bennett of University of Pennsylvania and Dr. Albert M. Maguire of Childrens' Hospital of Philadelhia (CHOP), whose work for more than 25 years on congenital blindness led to this ground breaking FDA approval. Join us to learn about the novel therapy, details on treatment procedure and recovery.

Full Transcript:

Priya Menon: Good afternoon and welcome to CureTalks. I'm Priya Menon, your host and today we are discussing the new FDA approved gene therapy for reversing blindness. Our guests are none other than the doctor couple responsible for this breakthrough approval. Dr Jean Bennett FM Kirby, Professor of Ophthalmology at the Perelman School of Medicine at the University of Pennsylvania and Dr Albert M Maguire, Clinical Associate of the division of Pediatric Ophthalmology at Children's Hospital of Philadelphia and Associate Professor of Ophthalmology at the University of Pennsylvania. Welcome to CureTalks, Dr Bennett and Dr Mcguire.

Dr Jean Bennett: Thank you very much. Happy to be here.

Priya: On our patient panel, we have Tabatha Mitchell, mom to Emory, an 11 year old little blind girl. Tabby and Emy have been changing what it means to be blind since Emy's diagnosis with LCA at NIH when she was three years old. They tirelessly advocate for rare disease research and blind children. We also have with us, Sarah Pettit, mom to nine year old Creed Pettit who has received the newly approved treatment Luxturna. So once again a very warm welcome to the guest and the audience. We will be addressing questions from the audience towards the end of the discussion. So if you have a question for the panelists, please email your questions to priya@trialx.com or you can also post your questions in the comments section on curetlaks.com. So beginning with the discussion. Dr Bennett, you bred a virus to carry the gene and Dr Maguire you injected it into a patient's eye and there was light. So this is an incredible journey. I would like to start with a very, very basic question Dr Bennett, what is a person who has Leber's Congenital Amaurosis actually be able to see and what causes this condition?

Dr Jean Bennett: Sure. I'm going to start with a general answer and then Al Maguire can be more specific. So there are at least 18 different genetic flavors of Leber's Congenital Amaurosis. Those are caused by different mutations in different genes and depending upon the exact genetic cause, people have different levels of light perception versus vision early in life. And, most of these genes actually caused damage or caused malfunction of the photoreceptors and that explains the visual findings. So for the form that was just at where we've been developing the gene therapy that just received FDA approval, that's a form called caused by mutations in a gene called RPE65. And I'll pass it over to Al to describe what people can see with this condition.

Dr Alfred Maguire: Well, the RPE65 helps load nerve cells with the molecule that captures light called 11-cis retinal and that's not functioning correctly in people with this particular form of Leber's Amaurosis. They have some vision and in some cases it's enough to get them, they're able to function and get around a bit when it's very, very bright. The way I think of it is, they have about one 10000th to one 50,000, the

sensitivity to light that, somebody with a normal retina would have. So it's as if you had a rheostat and you kept turning it down, turning it down so that they are only able to use about one-10000th of light that you or I and you can imagine that would make things difficult, especially when the hours of the day when it's not as bright out, that's sort of like an enforced curfew. There's also an issue with the central vision where there's some blurring because the resolution, the sharpness of vision in the center, is reduced as well. So overall it's dimmer and blurrier for people who are affected.

Priya: Luxturna is approved for people who carry the RPE65 mutation. And essentially we have a gene therapy which replaces this. So can you talk a little bit about what we will be exactly doing in the gene therapy?

Dr Alfred Maguire: So as you said, people who have this particular form of LCA would be candidates and what is done, which is very similar to the protocol followed in the phase three trial, the efficacy trial is, we establish whether people have enough functioning cells that they're going to get some useful vision as a result of the treatment, if you have no cells because over time they wasted away, it really doesn't make sense to do the treatment, it's not for people who don't have a functioning retina. So once it's established they have potential and enough cells, they undergo a procedure called vitrectomy where the back of the eye behind the pupil is centered with tiny instruments and the Luxturna, which is the gene therapy drug is injected under the retina and in the vicinity of the nerve cells and those nerve cells will take up the drug. So that's done in one eye and after anywhere from after one week, the other eye is treated as well. And while all this is being done with the surgery, the patient has a course of corticosteroids, something analogous to the dose you'd use for asthma or poison ivy. And that's to tamp down any possible immune response to the drug since it is a modified virus. Fortunately, we really never have seen a much, if any response to the, to the drug, in terms of inflammation.

Priya: So Dr maguire just mentioned the virus. So Luxturna is also the first AAV viral vector product approved for clinical use. So Dr Bennett, it would be really good if you could talk a little bit and explain what an AAV viral vector is, for the audience?

Dr Jean Bennett: Sure. And as you said, this is the first AAV, actually first viral vector that's approved for direct delivery for genetic disease in the United States. And we were very excited about this. And, so what this is, is essentially a shell, the virus as typically has a shell of proteins which package the genetic material, in this case DNA and viruses do what they do very well. They bind to cells and get into the cells and then the DNA or for other viruses, RNA makes its way to the nucleus where it takes up shop and starts in coding for the proteins that are encoded by that particular DNA strand. And so this recombinant virus is designed such that the bulk of the viral DNA that, for the wild type virus which can, can be copied in the cell is removed and instead it's replaced with the gene of interest, in this case, RPE65 connected to a switch which turns it on because without that the gene won't be expressed and it's packaged in this shell and, so the virus is delivered to what's called the subretinal space. It's a space adjacent to the six cells in the retina. It binds those cells in and then the DNA takes up shop in the nucleus, starts producing the normal copy of the RPE65 proteins, and that corrects the biochemical deficit in those cells, which then allows them to function and allows the person to see.

Priya: That's incredible! We're talking about the viral vector. So I would also like to right now read out a couple of questions that have just come in regarding the use of the virus for therapy. What happens to the copies of the bad genes that are being replaced in your eyes or bodies? That is one question that has just come in, Dr Bennett.

Dr Jean Bennett: Okay. So the bad genes stay there. In this particular disease, the bad genes are bad because they don't do anything. And so we don't need to remove them, they stay there and instead these cells gain, the new functioning jeans, which take care of the missing function.

Priya: Okay. There's another one, does the virus used in the gene therapy treatment make you sick in any other way. Does it do anything else to the body?

Dr Alfred Maguire: Yeah. So that, one of the most important things that, has been seen in AAV research and that's not just eyes that's systemically large organs in the body where they're using amounts of this virus that are thousands of times more than what we're using in the eye. It's very, very safe. AAV, which is Adeno Associated Virus, is a recombinant or a genetically engineered Parvo virus, which in humans does not cause any significant disease or some very esoteric condition called Fifth disease which most doctors have never seen and it's really a very mild viral illness. But that's the unmodified wild type adenovirus or adeno associated virus. This has been basically any pathogenic or toxic factors have been spliced out of the virus. And that the virus is basically engineered. So really all it does is it carries this piece of cargo, this new gene into cells and does not produce any sort of toxin. So it is extraordinarily safe.

Priya: Thank you. Dr. Macguire. You are already touched upon a little bit about the actual trial protocol. We are just trying to understand this a bit more, how much preparation should a patient or is a patient conducted through just before this injection or being treated with Luxturna?

Dr Alfred Maguire: Well, they're really, I mean, aside of the testing that's done before to make sure that they have the condition and there they have enough viable cells to treat, they're really no different than any other person who's having a retina procedure in terms of the standard things don't eat or drink after midnight or a few hours before the surgery, a general medical evaluation to make sure that there are no issues that might come up with the anesthesia. And really there's no significant difference. No major difference between any other type of eye procedure, eye surgery and Luxturna.

Priya: So how long does one procedure take, for example, treating with Luxturna. What is the time for the surgery or the injection..?

Dr Alfred Maguire: So, we know this well because we track time. So one way of putting it is in our original trial it took about two-thirds of the time it took to obtain an informed consent. The procedure takes about 50 minutes to perform from beginning to end. Certainly the entire day as I tell people while you have to show up to the hospital, you have to go through the checklist and you have to stay afterwards for a few hours to make sure that you're properly positioned so that the drug can soak into the retina. But the actual surgery itself about 50 minutes long.

Dr Jean Bennett: And being an observer of all of these surgeries, I just like to add that whole time of surgery is mainly for preparing to do the injection and the injection itself takes all of about 10 seconds.

Priya: Okay. That's great. So we also have with us Sarah Pettit, she's, as I just mentioned she is Creed Pettit's mom, Creed received Luxturna after it was approved, Sarah. Can you hear me?

Sarah Pettit: Yes

Priya: Hi Sarah. Great to have you here. Thank you for joining us. So Creed has had Luxturna treatment for both his eyes as I understand. So, were they administered together or one after another, can you give us a little bit detail about how the treatment went and how he's feeling now?

Sarah: Sure. He had his right eye done on March 21st and then we stayed down in Miami and he had his left side done on March 28th. And I mean he's doing great right now. He's very overwhelmed. It's a lot of things have. It's like teaching a toddler at this point, a lot of new things that he's never done, but he loves it. He wouldn't, he's very happy with what he says all the time. It's his new eyes, going out, like the doctors were saying earlier how there was a curfew for the time and that was so true. We were constantly fighting against the sun and now it doesn't. There's no rush. We can hang out outside even when the sun is setting, we can, he can still read books outside now. He can play outside now. And it's just a happier. He's much happier now that this is all done.

Priya: That's great to hear. Sarah, Dr Bennett. Can, this is a common question I've seen on forums and people asking whether people can get treated for only one eye?

Dr Jean Bennett: Theoretically people can be treated with just one eye. In our experience, at least in the clinical trials, everybody wanted their second eye injected particularly after the first eye was injected and they saw how much their vision improved. So yes, I would say it would be possible to inject one eye although the spark is recommending them both eyes be injected if they have enough cells that could merit the injection.

Priya: Yes. And Dr. Mcguire, you mentioned a week of time gap between one eye injection and the other eye being injected. Is that a reason or some considerations that we take into account when we decided this time?

Dr Alfred Maguire: So, there was a sort of a history behind the interval. So from a view, it's felt that if you give the exposure to the virus a very short period of time, you are not a priming the immune system to the second injection, so it's not going to act like a vaccination. So theoretically, the body, the immune system will look at two injections within a two week period of time is essentially being a one injection, one exposure to this antigen, to this virus. It turns out though that, one of the studies that we did earlier, so that patients who had the second eye treated in a safety study, the second eye treated sometimes years after the first eye had no untoward reaction and had no major or minor immunologic response. And, they also seemed to have just about as much improvement in their retinal function as they did when we had short injection intervals so that time period is really based on what was the minimum time between the two eyes, and just the idea that theoretically it might be better to have the second eye treated at a shorter interval to avoid an immune response.

Priya: Sarah, now that Creed is doing better, what are some of the cautions that you take, now that he's able to see and see better. That, as I said in his vision has improved. So are there any precautions that you are taking other than, of course as you just mentioned, you're teaching him like a toddler? So we just, like for the parents who are listening. .

Sarah: I take a lot less precaution than I did before. I have to say, I unfortunately regret coddling Creed so much. I've watched for nine years now, other parents with children of visually impaired all the way to blind children who can ride bikes and button their clothes. And I was a single mom for most of Creed's, most of the time, until recently. And so I kind of coddled Creed and protected him and did not want him to get injured and made sure that he kind of lived in his own little bubble and now that he had Luxturna, the one thing I do regret is not challenging him a little bit more before Luxturna because, it's definitely show me it's an for him, it's been very overwhelming for both of us because he no longer wants me to be right there over his shoulder and I'm having to learn how to step back. So, my precautions, I think the only thing that I am concerned about at this point in time is poking himself in the eye or something silly like that. There's nothing anymore when it comes to him running into the table or tripping over the dog or just walking into people in general. Those are not my concerns anymore at all. And none of that actually happens anymore either. So, it's been, it's like the tables have been turned on both of us, so, I definitely have to learn to let go at this point.

Priya: I wish, I hope that Creed is able to see his rainbow very soon. I've been reading about him wanting to see a rainbow.

Sarah: Yeah. And it has rained every day for months and we still haven't had one, so I was like, this is ridiculous. So hopefully soon.

Priya: Thank you. Thank you very much for sharing that. Dr Maguire, how long does it take actually patient for patients to recover and start being able to see an improvement in vision?

Dr Alfred Maguire: So, we will, we have actually documented that the retinal function can improve in the matter of days. We've done special testing of a pupil response, and basically as soon as we tested, I think around five days after the procedure, we were able to establish, in fact there's greater, much greater retinal sensitivity. It's interesting because there are certain tests you can't do immediately the post-operative period, but you can certainly ask patients what they're saying and what they think, and I was struck, I didn't

really believe it at first, but now I'm pretty sure it's true. I was struck on the day after surgery, patients complaining about how bright it was, and it's almost an overnight effect where they'll get much more sensitive and much the same lights, much easier for them. Fortunately, that almost overwhelming light sensitivity, that they get, patients get used to it after a few weeks and it sort of calms down. So it's their new norm.

Priya: Amazing actually to hear and I can't but help smiling if you could see me, I'm just smiling through this hearing both of you talk about this great, absolutely wonderful treatments that now we have for the people who have LCA. So Dr Bennett, what is the data that we have on how long the patients retain their improved vision?

Dr Jean Bennett: Well, we have more than a decade of data now going back to the very first patients who were injected, the thing is those first patients all receive different doses and so, there are different variables that could affect their response and all of them say that that first injected eye is retaining vision and we can measure that however, our best data comes from the second eye that was injected because all those second eyes got the same dose and we are now nearing the five year time point on those patients. And so far they have maintained all of the gains that we measured early on within 30 days after their injection.

Priya: Okay. So we do not have a comprehensive numbers like three years, four years or is that a progressive, are you noticing a progressive vision betterment as they're progressing over the years? Is that how it is?

Dr Jean Bennett: Well, the improvement, basically, it skyrockets early on. So by days 30, people are seeing immensely better than they were before the intervention. And that what we're measuring their plateaus in terms of light sensitivity and other aspects of vision. However, we think that there are changes going on that we don't measure in a clinical trial, such as understanding what you're seeing. For example, we had one patient who was with us in a car looking out the window and she had never seen tree branches before and like she had to be told what those were. And so she learned what tree branches were after her intervention. She, she'd learned what a reflection from a pond was. So these are a lot of abstract things that I think, the the person has to learn and that's not something that we can measure.

Priya: Alright. So would that actually, I think I should just know handover to Tabby. She has some questions for you, Tabby you are on air.

Tabatha Mitchell: And let me unmute on my end. Can you hear me?

Priya: Yes. Yep. Please ask your questions.

Tabatha: Once you lived in the blindness world and raising kids with low vision, I think we know what the term blindness is and how that's defined. We live in kind of this space where blindness and low vision is kind of like a spectrum. Can Dr Mcguire or Dr Bennett, either one, put a little bit of definition, put a little bit of description around what it means to be legally blind?

Dr Alfred Maguire: So legally blind means two different things. Essentially there's visual acuity which everybody is very familiar with – that's reading an eye chart and there's 20/20 vision, I think of it as a fraction 20 divided by 20 is 100 % normal central vision, whereas 20 over 200, which is the threshold for legal blindness, that would be 10%. Basically 20 divided by 200, 10% of normal central vision. And that's the threshold you cross. And that's considered legally blind for center vision. What's interesting is there are numerous retinal conditions, forms of Retinitis Pigmentosa and inherited retinal diseases where people have 20/20 vision and they're legally blind. Because having a good center visit is very important, but that represents only a tiny fraction, less than 4% of your entire visual field. So people are essentially with that sort of situation or looking through a long tube or a gunbarrel. But if your peripheral vision is constricted within 10 degrees center, which is a little bit harder concept to understand through. It's not like visual acuity. It's a more abstract test, but if it's constricted within 10 degrees of the center, the normal being out to about 70 or

80 degrees, then you're so constricted that it impairs your ability to walk around and be mobile, to drive, to even do things like reading. And that's considered also a criteria for legal blindness. So there's visual acuity, which is 2200 individual field which is within 10 degrees a constricted down to 10 degrees.

Tabatha: Now, is it the blindness or lack of vision that qualifies people to come into this study? So I know there was some mention earlier about having functional retinas, so working with a lot of the parents and a lot of the kids that are in the LCA community, but also with other genetic disorders that affect vision, one of the big questions that we hear a lot is if kids or adults are already blind, can they still be treated?

Dr Alfred Maguire: So it depends on the mechanism of the condition and I'll just comment on this RPE65. So the cells, the nerve cells are still there, but they lack the molecule to capture light. So it's like having a car and with no gas in it and that's it. I wouldn't say it's completely unique, but it's a very unique situation. A lot of forms of blindness, it's not, the cells are working correctly, but they are actually degenerated. They're worn out and they're not there anymore and that would require a different form of treatment than gene therapy because there are no cells to treat. I think maybe Dr Bennett could comment on other forms of how the biology works, the cause of the vision impairment.

Dr Jean Bennett: Yeah, it will. I would like to add that vision also depends upon the wiring being intact between the retina and the brain. And we don't know a huge amount about how long that wiring persists if somebody's retina is not functioning. There've been a number of very historic experiments studying this potential, this phenomena in newborn animals. But what we found with the RPE65 was actually surprising that, that even though the wiring between the retina and the brain hadn't been used for as long as 35, 40 years in one person when we could treat the retina, we could activate that wiring and allow it to provide the information to the brain, which of course is what we use to have vision. So we don't know the answer for the other conditions, whether the wiring is still viable, but we certainly have optimism based on our findings with the RPE65. And so for example, if there is somebody with LCA who only has light perception but has never had formed vision, it's a big question. We think that actually the wiring would be intact since it would be primed by having the light perception. But could we then get that person to be able to see a face? We don't know because we don't know if the brain is as malleable as we'd like it to be. But that's something that we feel that we've demonstrated in animal studies is possible. So we're hopeful that it will be effective for other forms of other genetic forms of early onset blindness.

Tabatha: One of the questions that comes up or one of the conversations that takes place a lot within blind communities is once they were identified as being blind or having light perception whenever they were younger or in their teen years, that they really don't have a lot of eye exams because they don't necessarily have a need to have them evaluated. They don't hurt, they just can't see. And so the question comes up of the discussion really kind of goes around the area of how do you determine if the retinas are non-functioning? I mean we tend to think of it as visually. If you can't see then they're not functioning, but what's the test that actually done and what's the advice that you guys give out to folks that may have an RPE condition since that's the one we're talking about today. And how do they go about determining if they might be a candidate?

Dr Alfred Maguire: So one of the answers to that is if you don't get an exam, you'll never know and you'll never have information like this. So if you, in the past people just sort of threw up their hands and said, what am I doing this for? There's no treatments available. And I just get the same answer over and over again and I, and to be honest, I'm completely sympathetic to that, because, I don't like to burden patients with unnecessary appointments. Everybody has a other things they'd rather be doing. However, things have progressed, things do progress. And, over the last 10 to 15 years, for instance, we now have new methods that we combined with a lot of the sort of standard testing that allow us to make better determinations as to whether a person, has the potential for vision. We can now actually image the retina with Tomography at extremely fine detail, almost like an optical biopsy. So we can tell if the cells are there, they may not be functioning because the biochemistry isn't working, that they don't have the proper molecules to capture light. But we know now we can do a very simple, painless, noninvasive tests to measure the thickness of the retina or even to see the individual nerve cells. So, it's a combination of things that we use to make the

determination. It's not just photographs or measuring visual acuity or visual fields. We use a sort of a consortium of things from our tool kit to be able to make that determination. And again, if you check in with the eye doctor periodically, you'll be able to take advantage of that kind of testing and the new technologies that come up.

Dr Jean Bennett: Yeah, and just to add to that, we find now that we're trying to develop gene therapies for other forms of blinding disease that we're running double time trying to get patients with these diseases to come in so that we can adjust our protocol to measure the sort of responses that would be appropriate for those various conditions, those are so called natural history studies and that's just because people have been told there's nothing you can do and have been lost to followup. And one more thing to add and maybe Dr Maguire wants to comment on this is for very young children, it's probably not a great idea to measure them too frequently because then they might get scared of going to the eye doctor. Now, I don't know if you want to comment on that.

Dr Alfred Maguire: Yeah, they need, I think they need a diagnosis, but I'm very much an advocate of not creating phobias because I'm the one who asked take care of the people with the phobias that they developed during childhood. So if you slowly ease people into the examinations and have a good pediatric trained ophthalmologist sort of, get the initial diagnosis, that's great. And, then if they can be treated, great, if not, then just sort of a check in every periodically to make sure that you're up on the new technology and if there are any clinical trials that come up, a they'll be made available to you

Tabatha: While we're talking about young kids, one of the questions that we hear within the groups is how do you guys evaluate, we talked a little bit, you talked a little bit about the acuity chart. How do you evaluate and what eye charts do you use for the really young kids?

Dr Alfred Maguire: So, I have been more and more impressed over time how sophisticated children are. So this study that led to Luxturna being approved included children from 3 years of age and older. And you would think three years of age, they had to do some pretty sophisticated stuff in terms of doing mobility courses at different light levels and then being able to do a visual field testing, etc. etc. And, by and large, most of the people who came for this study, we're able to do it and got included. So, our youngest was near three and theoretically that's a good age to do the treatments. So, but to answer your question specifically, there are many different it system, some of which don't even require a verbal answer from a child. There's something called a preferential looking that a masked observer will look to see if a child looks at a certain side of the chart more than the other. And they can tell the preference it usually gives an indication if they're able to see something. You can also ask a child to have their own card with the letters or figures on it and they actually will point to them on a card so that they don't have to give a verbal answer. And the very simple thing is a HOTV chart, which use just those four letters, what we, what we also call letters Opto types, but only those four letters and most children, if they can't read the entire alphabet can certainly be taught those four letters and that is a early sort of verbal chart that we use. But the kids are pretty smarter, a lot smarter than I sometimes let on.

Tabatha: Are you guys over the course of time, I think we were talking about 25 years. Are you seeing that the research is indicating that the treatment impact is potentially more robust when it, when the treatment is administered in young population, is that possible?

Dr Alfred Maguire: Jean?

Dr Jean Bennett: Yeah. So, our initial results in the animal models definitely show that, there was a much better response in those younger animals than the older ones. And it makes sense because this is also a degenerative condition. So over time the cells die off and there are less of them left to treat enough to respond. And so we hypothesized that we would see the same thing in humans. And, certainly the results of the intervention in individuals who have a wide range of ages in humans show that, generally the outcomes are people perform at a much higher visual level. The younger they are, probably reflecting the number of cells that they have, and this is sort of a generality. However it will take us more time to analyze all that data

in an objective fashion to clearly get a read out. But certainly when one would argue that would be, it would be more advantageous to a person to have vision over a longer span of their life than if they were treated when they were older.

Tabatha: So the burning question for a lot of folks out there that might have low vision or have no vision at this point in their lives and have kind of fallen off and not necessarily been to an eye doctor recently. How exactly do you determine if they have the RPE mutated genes that qualify or that has the treatment available now?

Dr Jean Bennett: It's really quite standard now for people to provide a saliva sample or a blood sample or, or any other tissue and skin sample, typically it's easiest to give us a live or a blood sample and then DNA is isolated from that sample and then screened for presence of mutations in a panel of genes and sometimes that panel is limited to those that cause early onset blindness, but there are now more than 265 different genes known that when they're mutated will cause blindness. So, the testing has gotten really, all inclusive in most cases, screening for a large number of potential gene mutations, which provides even more robust confidence that when you find a given mutation that that is the one and then typically one confirms that that is indeed the disease causing mutation by testing the parents and seeing if each one of them is a carrier of one of the mutant copies that the child has and that adds further confirmation to the genetic diagnosis. There are now many testing laboratories, not only in this country but around the world and in much faster feedback from the test results.

Tabatha: So representing a lot of the parents that are in the LCA group and the kids that are coming up through it as well. We're all pretty well versed and aware that it was the dogs that initiated a lot of this work that has moved through to a clinical trial and now moved into a treatment. So one of the questions that I hear among the kids in our group is how does the surgery that you're doing on your patients, your human patients that come in today, may, even though it's an FDA approved treatment, how does that compare with the surgery method and all of the things that you did with the dogs whenever you were in the research phase?

Dr Alfred Maguire: So the drug is a little bit different because it was modified. It was called humanized. Is that, is that the term we use? Yeah. So, so dog's DNA is very, very close, the gene is almost exactly the same but not quite exactly. So when we were testing the original dogs, it was more a canine based in terms of the gene that was introduced. So the surgery is essentially the same, you take a small to place it under the retina and inject the medicine. The actual mechanics are a lot different because imagine dogs have their eyes on the side of their head. They have this big snout in front of them, which would, if you were in a human operating theater that would hit the microscope, that would be a bit of a problem. So a lot of it was just little sort of a mechanical things to properly position the animals and just compensate for a different morphology, different look to the face into the snout. But, when it came down to the actual treatment, yeah, they had the injection under their retinas exactly like the humans and they respond and amazingly similar way to.

Dr Jean Bennett: Yeah, I'd like to add it to. Two of those initially treated dogs are now living at our house. At the end of the experiment when we had all of our data, we decided they had given us such great information, had been so valuable and we loved them in addition. So we actually went all the way to the provost at the university to be able to adopt them and give them a good home.

Tabatha: Can you, can you share with everybody out there, especially the kids that are listening what are the dog's name and what type of dogs are they?

Dr Alfred Maguire: So Mercury and Venus. Venus is the mother, Mercury is the son and they are Swedish Briard that were bred by Christina Nordstrom. So, who is a Swedish veterinarian. And they are very unusual, you know, you can google image the Swedish Briard. In fact, I think there are pictures are probably gonna come up, but they're very unusual and very beautiful looking dogs and yeah, they run around the backyard and they look, bark and move around just like any other dog I've ever had.

Dr Jean Bennett: And they're very, very sweet. If any child listening would like to meet them, they're always welcome to meet. I'm in philadelphia,

Tabatha: Now a curious question, just as dog owners out there, once they receive the treatment, you had mentioned that they had the same type of rapid pickup. Did you find that there were odd little things that you kinda had to reteach them as we were talking about with Creed and in some of the other things that we're seeing go on?

Dr Jean Bennett: Yes. So these animals were born and raised in an animal facility which is on one floor and there are no windows, no grass. So the first time that I got approval to take the dogs home, I've brought them outside. They saw grass and they're prying it because they'd never seen anything with that texture or shape color before. And then stairs were a new phenomenon for them. They'd never seen stairs and it, it, they had to kind of figure out, oh, this is how you walked downstairs now. No, you'd never know there was a problem, but they hadn't had never had that experience. And it's not a problem for them because they can see the stairs, but it was a new experience.

Tabatha: That's wonderful. Thank you for sharing that.

Priya: Thank you Tabby. That was a great set of questions. Dr Maguire and Dr. Bennett we'll take some questions from the audience. Now we have a whole lot of questions on the website. I see the most common one is if we see that the vision is reducing again, do we do this procedure once more?

Dr Alfred Maguire: So, we don't have an answer for that just because I guess the good problem, we haven't definitively seen in the phase three trial any reduction in vision. And I guess part of the thing is why is the vision being reduced? So when you create one of these blabs, one of the, when you, when you inject onto the retina, we're not actually injecting under the entire retina, that would require, I mean that would be more of a risk and it would require a lot more material. We try and treat the most relevant parts of the retina for day to day vision, the center vision and things you used to walk with. So it may be that the areas that don't receive the drugs aren't working quite as well and you might be able to measure that as a slight decrease over time because those areas aren't receiving the drug. But I don't know that would be a good reason to go back and inject since those parts of the retina really aren't used very much for vision though we can still measure. But it depends what the reason that the decrease in vision and why it happens. It's conceivable that we might re-inject or do additional injections if it was a case that vision were decreasing and we could improve things by just one injection.

Priya: Thank you Dr Maguire. We have some questions regarding the age or the range of age that you can, that patients are selected for, for the treatment of Luxturna. Also asking if newborn screening is possible and also if adults can be treated?

Dr Alfred Maguire: Jean so why don't you take the newborn screening and I'll talk about the age range.

Dr Jean Bennett: Sure. Okay. So for newborn screening, yes indeed, it is possible to do that. At present newborn screening is not covered by insurance, however, it's possible to do that on your own. And that could again be done from a tiny blood sample or saliva sample, or if skin is removed for some reason that can be tested. However, I would like to add that, that if people, if the individual is found to have an RPE65 mutation, the current guidelines for delivery of Luxturna required that somebody be one year old or older so that there is a large time window during which this testing could occur prior to a treatment.

Dr Alfred Maguire: So, in terms of the age range, as Jean said it's a one year and older, which is, it was a thought that at that point, the is enough that the treatment can be administered with a minimal increase in risk. And then in addition there's nerve cells in the retina that are done replicating. So there would be no dilution of the drug dilution into more and more cells as they divide. In terms of the oldest, it again, it all depends, there are people that we've seen who were in their third, fourth decade of life who actually have a population of cells that are still there and can potentially respond. So again, it depends on it. There is no

upper age limit as long as there are viable cells that can be better left and that can be demonstrated. Unfortunately there are some people we've seen who are in their fourth, fifth decade of life and, and honestly, they just don't have any population of nerve cells left. And for them to go through a procedure like this would just be, it doesn't make sense and it would actually be a no advantage to them at all.

Priya: Thank you Dr Maguire. Another question, I think quite a few questions on whether this kind of approach can be used to intervene in blindness conditions which are due to other mutations and especially your research in CEP290?

Dr Jean Bennett: So, there is a, a great deal of laboratory research that is ongoing all over the world looking at ways of intervening with other forms of retinal degeneration, including CEP290. The particular challenge with CEP290 is that the gene is very large and so it does not fit within the cargo capacity of the adeno associated virus, the AAV, that we spoke about, but there are some other strategies that are being considered and including strategies of allowing this gene to fit into that small cargo capacity. So, back to the original question, the answer is yes. If the gene can fit in, it can be delivered through the AAV, to the appropriate retinal cells. It should work to intervene with the condition and provide vision. And indeed, proof of concept has occurred in multiple genes in animal models in the laboratory and is forming a pipeline that hopefully will translate into human clinical trials in the near future.

Priya: Thank you Dr Bennett. I would like to read out a comment that has just been posted to both of you. It says I'm so grateful for this groundbreaking technology and the people who have made this possible. I have a 10 year old daughter who is at her two weeks post-op in one eye and one week post-op on her other eye today. We have already noticed big gains in dim light. She's seeing things in a whole new light and so excited about her new perspective. As a mom to see her point to the sky and say I see clouds. nothing is more beautiful. So thank you. Thank you. Thank you. That's what she writes. So Dr Bennett and Dr Maguire, I think you have made many, many children happy, their parents happy. 25 years of research on congenital blindness and that's awesome. Finally brought in this approval of Luxturna and thank you so much, we are almost at the end of our hour. Thank you so very much for your continuous persistent efforts, your time and sharing all this information with us. I would also like to thank Tabby and Sarah for participating and Tabby for those excellent questions for your group and also thank University of Pennsylvania and Children's Hospital of Philadelphia and the audience. This talk is recorded and will be available on curetalks.com, so please visit our website for details on more upcoming talks. Thank you and have a great evening everyone. Thank you.